General

Guideline Title

Aflibercept for treating diabetic macular oedema.

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Aflibercept for treating diabetic macular oedema. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jul. 46 p. (Technology appraisal guidance; no. 346).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Aflibercept solution for injection is recommended as an option for treating visual impairment caused by diabetic macular oedema (DMO) only if:

- The eye has a central retinal thickness (CRT) of 400 micrometres or more at the start of treatment and
- The company provides aflibercept with the discount agreed in the patient access scheme

People whose treatment with aflibercept is not recommended in this National Institute for Health and Care Excellence (NICE) guidance but was started within the National Health Service (NHS) before this guidance was published should be able to continue aflibercept until they and their NHS clinician consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Diabetic macular oedema (DMO)

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Ophthalmology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To assess the clinical effectiveness and cost-effectiveness of aflibercept for treating diabetic macular oedema (DMO)

Target Population

Adults with visual impairment due to diabetic macular oedema (DMO)

Interventions and Practices Considered

Aflibercept

Major Outcomes Considered

- Clinical effectiveness
  - Mean change from baseline to 52 weeks in best corrected visual acuity (BCVA)
  - Proportion of patients gaining 10 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters and 15 or more ETDRS letters from baseline to week 52
  - Mean change in central retinal thickness (CRT) from baseline to week 52, as assessed on ocular coherence tomography (OCT)
  - Vision-related quality of life (assessed by the National Eye Institute Visual Functioning Questionnaire-25 [NEI VFQ-25])
  - Quality of life (assessed by the EuroQol-5 dimension health questionnaire [EQ-5D])
  - Adverse effects of treatment
  - Mortality
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Aberdeen Health Technology Assessment (HTA) Group (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Searches

The company states that literature searches were undertaken in October 2013 and updated in August 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, PubMed and CENTRAL as well as the major clinical trials registers and relevant conference proceedings for the last six years. Full details of the search strategies are included in the company's submission (see the "Availability of Companion Documents" field) and are reproducible.

The searches were designed to identify all trials for diabetic retinal disease without specifying aflibercept or any of the relevant comparators. As such the search was very broad and therefore would be expected to be highly sensitive. The search strategies followed the same structure: a combination of the search facets *Diabetes Mellitus* with *Macular Degeneration* or *Macular Oedema* and then addition of the *Diabetic Retinopathy* facet using the Boolean operator OR. Appropriate randomised controlled trial (RCT) filters were used in MEDLINE and EMBASE. Specific additional searches for adverse events were not undertaken.

There is some concern, however, that only "oedema" was used throughout the searches and not the most commonly used spelling "edema". In MEDLINE, the correct MeSH is "Macular Edema"/. However, the company's search used "Macular Oedema". This term returned 0 hits when replicated by the ERG. Nevertheless, the submission indicates that 4542 hits were returned in the initial MEDLINE search and it is unclear how this was achieved. In EMBASE the incorrect term was again used but was automatically mapped to the correct term. This error was also applied to the text word searching throughout the searches in all databases and conference abstract searches. This error could have affected the sensitivity of the search. However, apart for this error, a comprehensive list of search terms and combinations were used and, to some extent, may have compensated for this omission.

Inclusion Criteria

The inclusion criteria used in the company's systematic review of clinical effectiveness are presented in the table below.

Table. Inclusion Criteria Used in Systematic Review of Clinical Effectiveness

Population	Patients with DMO
Intervention	• Eylea (VEGF Trap Eye/Aflibercept/AFB) • Anti-VEGF treatments (any including ranibizumab/Lucentis/RBZ, bevacizumab/Avastin/BVZ, pegaptanib/macugen) • Intravitreal steroids (any including triamcinolone, fluocinolone [Iluvien], dexamethasone [Ozurdex] and implants) • Laser treatments • NOTE: the intervention should be to treat the DMO not to treat cataracts • The above interventions can be included if combined with other treatments (e.g., eye drops) except the exclusions
Comparator	• Placebo, best standard care, masked control, sham, eye drops • Any intervention (from those listed as interventions) • NOTE: this can be a single treatment/implant

Outcomes	• Number of injections/treatments
	• Number of visits/assessments
	• Best corrected visual acuity (BCVA) (Mean change from baseline, mean average change from baseline, as measured by ETDRS score or Snellen equivalent)
	Visual acuity (% of patients who gain/lose outcome vs. baseline):
	  • Loss of ≤15 letters in ETDRS score (maintained vision)
	  • Loss of ≥30 letters ETDRS score (severe vision loss)
	  • Loss of ≥15 letters ETDRS score (moderate vision loss)
	  • Gain of ≥15 letters
	  • 20/40 vision or better (Snellen chart)

	• 20/200 or worse (Snellen chart) • Gain ≥0 letters • Gain ≥10 letters • Gain ≥30 letters • Reduction in laser use • Contrast sensitivity • Change in choroidal neovascularisation (CNV) • Optic disc area • Area of lesion • Size of leakage • Greatest linear dimension • Fluid on OCT • Presence of dye leakage • Eyes with dry lesion • Change in total lesion size • Change in central foveal thickness, mean change from baseline • Health-related quality of life (EQ-5D, NEI VFQ-25, other scales) • Treatment discontinuation • Serious adverse effects (all SAE, all ocular SAE, death, endophthalmitis, uveitis, retinal tear, diabetic macular/retinal oedema, reduced visual acuity, vitreous haemorrhage, corneal abrasion, any others) • Adverse events (all AE, all ocular AE, all non-ocular AE, retinal detachment, retinal ischaemia, lens damage, all grades ocular inflammation, eye pain, increased ocular pressure, retinal degradation, macular oedema, cataract, neovascularisation, any others) • Serious non-ocular adverse events (all, non-fatal cardiac infarction, non-fatal stroke, non-ocular haemorrhage, hypertension, serious systemic events, arterial thrombotic events, venous thrombotic events)
Study Design	• Published and unpublished randomised controlled prospective clinical trials • Dose or frequency comparison trials • Ad-hoc analyses of RCT data • Crossover RCTs
Language Restriction	None

Note: AFB, aflibercept; BVZ, bevacizumab; DMO, diabetic macular oedema; EQ-5D, EuroQol-5 dimensions; ETDRS, early treatment diabetic retinopathy study; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; OCT, ocular coherence tomography; RBZ, ranibizumab; RCT, randomised controlled trial; SAE, serious adverse event; VEGF, vascular endothelial growth factor

It is worth noting that some of the listed outcomes (i.e., change in choroidal neovascularisation; optic disc area; area of lesion; size of leakage; greatest linear dimension; change in total lesion size) seem to relate to other condition (exudative age-related macular degeneration [AMD]) and not to diabetic macular oedema (DMO). Furthermore, *retinal degradation*, in the list of adverse events, does not describe a retinal disease or complication and it is a term not commonly used in current ophthalmic clinical practice.

Identified Studies

The company's submission included two RCTs, VISTA and VIVID, comparing aflibercept (2 mg every 4 weeks or every 8 weeks after five initial monthly doses) versus focal laser photocoagulation.

Cost-effectiveness

ERG Comment on Company's Review of Cost-effectiveness Evidence

Objectives of the Cost-effectiveness Review

A systematic review was carried out by the company to identify relevant cost-effectiveness studies.

The company states in the submission that literature searches for cost-effectiveness studies were undertaken in October 2013 and subsequently updated in August 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, EconLIT and National Health Service Economic Evaluation Database (NHS EED) as well as relevant conference proceedings for the last six years. Full details of the search strategies are included in the company's submission and are reproducible.

The search strategies followed the same structure as for the clinical effectiveness searches and replace the RCTs filters with appropriate cost-

effectiveness filters. Once again, however, the term 'edema' was not used and this omission had the potential to impact on the sensitivity of the search.

With regard to quality of life data, the company conducted literature searches in February 2014. An appropriate range of databases were searched: MEDLINE, MEDLINE in Process, EMBASE, EconLIT and NHS EED. Full details of the search strategies are included in the company's submission and are reproducible. The search strategies followed the same structure as for previous searches with the inclusion of appropriate quality of life/utilities filters. In addition specific utilities for adverse events and blindness were sought. For all searches, both 'oedema' and 'edema' had been used correctly. These searches were judged by the ERG to be adequate and comprehensive.

Inclusion/Exclusion Criteria of the Cost-effectiveness Review

Only full-published economic evaluations were eligible, including studies based on models or performed alongside clinical trials. General cost of illness, economic burden, sot-minimisation and budget impact studies were not considered for inclusion.

Studies Included in the Cost-effectiveness Review

The systematic literature review identified 10 studies directly related to the decision problem. The company submission provides an overview of these ten studies. The TA274 ranibizumab for diabetic macular oedema (DMO) is perhaps the most immediately relevant of all identified studies. The submission draws a number of values from this. The Haig et al. study, which models the cost-effectiveness of ranibizumab for DMO in the Canadian setting, is also particularly relevant.

Number of Source Documents

Clinical Effectiveness

- Two ongoing randomised controlled trials (RCTs) (VISTA and VIVID) comparing aflibercept (2mg every 4 weeks or every 8 weeks after five initial monthly doses) versus focal laser photocoagulation were included in the review.
- A total of 11 studies contributed to the network meta-analysis.

Cost-effectiveness

- The systematic literature review identified 10 studies directly related to the decision problem.
- The manufacturer presented an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform an assessment of the manufacturer's submission on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for this technology appraisal was prepared by the Aberdeen Health

Technology Assessment (HTA) Group (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Critique of the Methods of Review(s)

Critique of Data Extraction

The company used the methods recommended by the German Institute for Quality and Efficacy in Health Care (IQWiG), the Cochrane Collaboration and the University of York Centre for Reviews and Dissemination (CRD) to assess current evidence. The methods described in these publications are, in general, considered appropriate.

Title/abstract screening, full-text screening, and quality assessment were all carried out by two independent reviewers with a third reviewer acting as arbitrator, where necessary. Data extraction was carried out by one reviewer and checked by a second reviewer. These procedures are all considered appropriate. The information and data extracted from the included studies are detailed in the company's submission and considered appropriate, even though it is not clear whether they were specified *a priori*.

Quality Assessment

The company adopted the criteria specified by the CRD for the assessment of the risk of bias in the VISTA and VIVID randomised controlled trials (RCTs). The criteria, which involve assessment of selection bias, performance bias, detection bias, attrition bias and reporting bias, are considered appropriate by the ERG.

The VISTA and VIVID RCTs were based on the same methodology, the quality of which is considered adequate. In particular, the randomisation process is appropriate and has proved to be successful (i.e., baseline demographics and disease characteristics were balanced across the intervention groups). The company maintain that concealment was adequate based upon randomisation being via interactive voice response system/interactive web response system (IVRS/IWRS) and the study being double masked. This information is considered insufficient to assess whether concealment of treatment allocation was performed adequately. Study personnel and participants were masked throughout the trials, with the exception of the unmasked personnel who administered the study drug but took no other part in the study. The ERG considers this masking strategy appropriate.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the CRD criteria. Results are presented in Table 6 of the ERG report.

Refer to Section 4.1.6 in the ERG report for more information about quality assessment.

Critique of Trials of the Technology of Interest, Their Analysis and Interpretation (and Any Standard Meta-analyses of These)

Meta-analysis of VIVID and VISTA

The submission includes standard meta-analyses of the results of the VISTA and VIVID trials for a number of relevant outcomes. The results are presented initially in tabular format (in the company's submission) using both fixed and random effects models. Some of these results are also presented as forest plots within the indirect comparison section of company submission. The meta-analysis comparisons are made exclusively between aflibercept 2Q8 regimen and laser. This choice is justified by the fact that aflibercept 2 mg intravitreal every 8 weeks (2Q8) is the licensed aflibercept dose in the UK and that approved by the European Medicines Agency (EMA).

Critique of Submitted Evidence

It is worth pointing out that main entry criterion for VIVID and VISTA was a central retinal thickness (CRT) in the 1 mm central retina, as assessed by ocular coherence tomography (OCT) (not determined whether spectral domain or time domain OCT). Thus, at entry, patients may or may not have fulfilled the standard definition of clinically significant macular oedema (CSMO). CSMO was, however, used as re-treatment criterion for laser photocoagulation therapy. Thus, one could argue that the initial laser treatment was not given based on the presence of CSMO while the re-treatments were; the rationale for this is unclear to the ERG. It is not specified either whether fluorescein angiography was obtained prior to laser treatment to guide laser (as recommended by the Early Treatment Diabetic Retinopathy Study [ETDRS]).

Critique of the Indirect Comparison and/or Multiple Treatment Comparison

Critique of Network Meta-analysis

The company provided a network meta-analysis for both fixed and random effects. Although the company provided the WINBUGS codes for the model and the source data, they did not provide information on the initial values used, or the process of running the model. The ERG were able to

determine from the model results provided in the submission's Appendices that the company had used a burn-in of 20, 000 iterations, followed by 20,000 iterations, which acted as updates for the model. However, it was not clear if this was 20,000 consecutive updates or say 100,000 using a thinning parameter of five. Models can be sensitive to the initial values and because the company did not provide their initial values or full details on the iterative process, in some cases, the ERG were unable to replicate the results. The ERG independently extracted source data from the references and matched them with those provided by the company.

Refer to Section 4 and Tables 4 to 19 in the ERG report (see the "Availability of Companion Documents" field) for additional information on clinical effectiveness analysis.

Cost-effectiveness

Summary and Critique of Company's Submitted Economic Evaluation by the ERG

Model Structure

A *de novo* Markov model with a monthly cycle was developed by the company. This is a bilateral vision model with each eye being in one of eight possible health states which are in the main 10 ETDRS letters wide. This results in a total of 64 possible vision states plus the additional absorbing health state of death. The health states for each eye are based upon the ETDRS letter ranges (see Table 22 of the ERG report).

Patients enter the model having at least one eye being treated for diabetic macular oedema (DMO). Of these patients 46.5% are assumed to be bilateral at baseline. An additional 10% of the remainder develop fellow eye DMO involvement at the start of years 2, 3, 4 and 5. It is assumed that 50% of the fellow eyes with DMO at baseline will be treated at baseline, and that 50% of incident fellow eye DMO will be treated at incidence. The other 50% of fellow eyes with DMO are assumed not to be treated.

For eyes that are treated there is an initial efficacy phase of one year followed by a maintenance phase of 4 years. Treatments are associated with a treatment specific discontinuation rate during the first 5 years of treatment. After 5 years all treatment stops.

The clinical effectiveness estimates for the efficacy phase are based upon applying the relative risks of the network meta-analysis to the rates of improving and worsening by at least two health states and by one health state in the pooled VIVID/VISTA laser arm. During the four year maintenance phase treatment is assumed to continue. Eyes that remain on treatment retain stable vision.

When treatment stops, due to either discontinuation or the end of the maintenance phase, the eye is subject to a monthly 1.15% probability of deteriorating by one health state. This is based upon the 3.5% quarterly rate of deterioration used within the single technology appraisal (STA) of ranibizumab for DMO.

Non-DMO eyes are subject to a monthly 0.17% probability of deteriorating by one health state.

Refer to Sections 5 and 6 in the ERG report (see the "Availability of Companion Documents" field) for additional information on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Care Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are

not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE Web site. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

Summary of Appraisal Committee's Key Conclusions

Availability and Nature of Evidence

The Committee noted that the company model was well structured and accounted for vision loss in both the better seeing eye and worse seeing eye. The Committee concluded that the company model was acceptable for assessing the cost-effectiveness of aflibercept.

Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model

The Committee heard from the Evidence Review Group (ERG) that the annual cost of blindness had been applied monthly and had not been discounted in the company's model.

The Committee acknowledged that the summary of product characteristics for aflibercept and ranibizumab states a reduced dosing interval after the first 12 months, and agreed that there is uncertainty around the average number of aflibercept injections that a person would receive after the first 12 months. Given that there is no robust clinical data for estimating the average number of aflibercept injections in year 2, the Committee concluded that the economic modelling of treatment should be based on trial data, and that a sensitivity analysis that included an equalisation of the number of injections of aflibercept and ranibizumab in year 2 was an acceptable basis for its decision-making.

The Committee considered the company's rationale and the ERG's critique for increasing the cost of a laser administration from £139 to £194. The Committee concluded that it was appropriate to have an equal cost for both a laser and intravitreal injection administration and agreed to increase the cost of laser administration.

Incorporation of Health-related Quality-of-Life Benefits and Utility Values. Have Any Potential Significant and Substantial Health-related Benefits Been Identified That Were Not Included in the Economic Model, and How Have They Been Considered?

The ERG considered the literature-sourced values from Czoski-Murray et al. (2009) were not ideal because the values apply only to the bilateral best corrected visual acuity (BCVA), which meant that the company had to use an adjustment factor to calculate the utility values of the worse seeing eye. The Committee acknowledged the company's reason for using Czoski-Murray et al. (2009) utility values in its submission (that is, consistency with other NICE technology eye appraisals). It also acknowledged that sensitivity analyses using the utility values from Brown (1999)

and Brown (2000) were included. It concluded that the Czoski-Murray et al. utility values, although not ideal, were an acceptable basis for its decision-making.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

The Committee heard from clinical experts that in clinical practice the choice of treatment depends on the central retinal thickness (CRT) and so it considered separately the cost effectiveness of aflibercept compared with laser in people with a CRT of less than 400 micrometres and in people with a CRT of 400 micrometres or more.

What Are the Key Drivers of Cost-effectiveness?

The results of the ERG sensitivity analyses over various ranibizumab discounts showed incremental cost-effectiveness ratios (ICERs) up to £1,260,695 per quality-adjusted life year (QALY) gained (100% ranibizumab discount using the EuroQol-5 dimension [EQ-5D] generalised estimating equation analysis). The ERG noted that in these analyses the choice of quality-of-life values had the biggest effect on the ICER.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

For aflibercept compared with ranibizumab in the whole trial population, the ICER is within the range considered to be a cost-effective use of National Health Service (NHS) resources (below £20,000 per QALY gained).

The Committee then considered the revised base-case ICER for aflibercept compared with laser in the whole trial population that incorporated the Committee's preferred assumption of an increased cost of laser administration. The Committee noted that the ICER was £33,100 per QALY gained.

The Committee noted that the ICER for the less than 400 micrometres CRT subgroup was £49,400 per QALY gained for the comparison of aflibercept with laser. It considered the revised ICER using the increased cost of laser administration, which was £48,300 per QALY gained.

The Committee considered the ICERs for aflibercept compared with laser in the subgroup of people with CRT 400 micrometres or more. The ICER for people with a CRT of 400 micrometres or more was £22,000 per QALY gained. It considered the revised ICER by the ERG using the increased cost of laser administration, which was £21,400 per QALY gained.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD) and were provided with the opportunity to appeal against the final appraisal determination (FAD).

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered evidence submitted by the company on aflibercept and a review of this submission by the Evidence Review Group (ERG). The main clinical effectiveness evidence came from two ongoing randomised controlled trials (RCTs). For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of aflibercept for treating diabetic macular oedema (DMO)

Potential Harms

In the summary of product characteristics the most frequent adverse reactions to aflibercept treatment include subconjunctival haemorrhage (bleeding under the membrane covering the white of the eye), reduction in visual acuity, eye pain at the injection site, an increase in intraocular pressure and cataract formation.

For full details of adverse reactions and contraindications, see the summary of product characteristics.

Contraindications

Contraindications

For full details of contraindications, see the Summary of Product Characteristics.

Qualifying Statements

Qualifying Statements

- This guidance represents the views of the National Institute for Health and Care Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- Section 7(6) of the National Institute for Health and Care Excellence (NICE) (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, National Health Services (NHS) England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.
- When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has diabetic macular oedema (DMO) and the doctor responsible for their care thinks that aflibercept is the right treatment, it should be available for use, in line with NICE's recommendations.

- The Department of Health and Bayer Pharma have agreed that aflibercept will be available to the NHS with a patient access scheme, which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to lesley.gilmour@bayer.com.
- NICE has developed tools to help organisations put this guidance into practice (listed below).
    - Costing template and report to estimate the national and local savings and costs associated with implementation (see also the "Availability of Companion Documents" field).

Implementation Tools

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Aflibercept for treating diabetic macular oedema. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jul. 46 p. (Technology appraisal guidance; no. 346).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Jul

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Andrew Stevens (*Chair of Appraisal Committee C*), Professor of Public Health, University of Birmingham; Professor Eugene Milne (*Vice Chair of Appraisal Committee C*), Director of Public Health, City of Newcastle upon Tyne; Dr David Black, Medical Director, NHS South Yorkshire and Bassetlaw; David Chandler, Lay Member; Gail Coster, Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust; Professor Rachel A Elliott, Lord Trent Professor of Medicines and Health, University of Nottingham; Professor Wasim Hanif, Professor in Diabetes and Endocrinology, University Hospital Birmingham; Dr Alan Haycox, Reader in Health Economics, University of Liverpool Management School; Emily Lam, Lay Member; Dr Allyson Lipp, Principal Lecturer, University of South Wales; Dr Claire McKenna, Research Fellow in Health Economics, University of York; Dr Patrick McKiernan, Consultant Paediatrician, Birmingham Children's Hospital; Dr Andrea Manca, Health Economist and Senior Research Fellow, University of York; Dr Suzanne Martin, Reader in Health Sciences; Dr Iain Miller, Founder and Chief Executive Officer, Health Strategies Group; Dr Paul Miller, Director, Payer Evidence, AstraZeneca UK Ltd; Professor Stephen O'Brien, Professor of Haematology, Newcastle University; Professor Peter Selby, Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust; Professor Matt Stevenson, Technical Director, School of Health and Related Research, University of Sheffield; Professor Robert Walton, Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry; Dr Judith Wardle, Lay Member

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the National Institute for Health and Care Excellence (NICE) Web site.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Aflibercept for treating diabetic macular oedema. Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jul. 9 p. (Technology appraisal guidance; no. 346). Available from the National Institute for Health and Care Excellence (NICE) Web site .

- Aflibercept for treating diabetic macular oedema. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jul. (Technology appraisal guidance; no. 346). Available from the NICE Web site .
- Fielding S, Cummins E, Cruickshank M, Fraser C, Lois N, Brazzelli M. Aflibercept for the treatment of diabetic macular oedema: a single technology appraisal. Aberdeen (UK): Aberdeen HTA Group; 2014 Dec. 166 p. Available from the NICE Web site .
- Aflibercept for treating diabetic macular oedema. Single technology appraisal. Manufacturer's submission. Bayer; 2012 Jun. 431 p. Available from the NICE Web site .

Patient Resources

The following is available:

- Aflibercept for treating diabetic macular oedema. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2015 Jul. 2 p. (Technology appraisal guidance; no. 346). Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub and eBook formats from the NICE Web site .

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